

REMARKS

Applicant respectfully requests reconsideration. Claims 1-27, 32, 53, 54, 76, 78, 158, 175 and 195 were previously pending in this application. Claims 1-9, 11, 12, 27, 32, 53, 54, 76, 158, 175 and 195 are withdrawn from consideration. Claims 10, 13, 14, 15, and 78 have been amended. Support for this amendment is found throughout the application, at least on page 4, lines 5-9 and page 50, lines 3-4. Claims 13-15 have been amended to remove dependency to claims no longer pending. Withdrawn claim 195 has been amended to correct a typographical error. New claims 198 and 199 have been added. Support for these claims is found at least on page 144, Example 3 and pages 146-147, Table 8. No new matter has been added.

As a result, claims 10, 13, 14-26 and 78 are pending for examination with claims 10 and 78 being independent claims.

Elections/Restrictions

The Examiner has acknowledged that Applicants' election of a single sequence was with traverse. The Examiner, however, did not find Applicants arguments persuasive. According to the Examiner, "The selection of a single sequence is not unreasonable because the sequences have different structures that would necessarily confer different functions" (see Office Action, page 2).

Applicants respectfully disagree and reiterate that the search of sequences SEQ ID NOs.: 304-310 and 356 would not impose a serious burden on the Examiner. As disclosed in the application, phage display libraries, such as Lin20 which includes the polypeptide sequences SEQ ID NOs.: 304-310 and 356, were created to provide a phage population (library) displaying a vast number of different but structurally related amino acid sequences. The amino acid variations are designed to alter the binding properties of the binding peptide or domain without significantly altering its structure (see page 50, lines 18-27). The Lin20 library was constructed to display a single linear peptide in a 20-amino acid template. The amino acids at each position in the template were varied to permit any amino acid except cysteine (see page 50, lines 2-4). The function of these polypeptides is to bind KDR or VEGF/KDR. Binding affinities are disclosed in Table 8, page 145 to page 147, for the selected Lin20 variants (SEQ ID NOs: 304-310). Applicants therefore assert that the sequences are structurally related and confer the same or similar function, and that a search

of these sequences would not impose an unreasonable burden on the Examiner.

Applicants timely traversed the Restriction Requirement and reserve the right to petition the Restriction Requirement under 37 C.F.R. § 1.144 according to MPEP § 818.03(c).

Priority

The Examiner has indicated that Applicants' priority claim under 35 U.S.C. § 119(e) has been accepted. The priority date of March 1, 2002 is acknowledged.

Information Disclosure Statement

The Examiner has indicated that the information disclosure statements submitted on July 14, 2004, January 31, 2006 and July 27, 2006 are under consideration.

Objections to the Specification

The Examiner has objected to the specification. Applicants address each point raised by the Examiner in turn.

The Examiner objected to the related applications section on page 1 of the application. Applicants have amended this section to recite Abandoned to reflect the current status of the applications as requested.

The Examiner suggested that Applicants describe the abbreviation for spacer "JJ" at its first occurrence in Figure 1. Applicants have amended the description of Figure 1 to include this description. Support for this amendment is found throughout the specification, at least in the description of Figure 3, page 31.

The Examiner noted that the SEQ ID NO.: identifier was missing from the sequence disclosed on page 34, line 1 of the specification. Applicants have amended this paragraph to add the sequence identifier SEQ ID NO.:377. Support for this amendment is found at least on page 33, line 28, and in the sequence listing as filed.

Applicants have amended the specification to correct the typographical errors highlighted by the Examiner.

No new matter has been added.

Accordingly, withdrawal of this objection is respectfully requested.

Claim Objections

The Examiner has objected to claim 14 for an informality. Applicants have amended the recitation of “and amide bond” to “an amide bond” to correct the typographical error. No new matter has been added.

Accordingly, withdrawal of this objection is respectfully requested.

Double Patenting Rejection

The Examiner rejected claim 78 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 11-20 of copending US Patent Application Publication US 2004/0018974 A1 (SN 10/379,287). This rejection is a provisional one because the claims have not yet been patented.

Applicants therefore defer substantive rebuttal of this provisional rejection until one or more claims are found allowable.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 10 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically the Examiner suggests spelling out KDR and VEGF at the first occurrence in the claim. Applicants have amended claim 10 to add the description for KDR (kinase domain region) and VEGF (vascular endothelial growth factor). Support for this amendment is found throughout the application, at least on page 4, lines 5-9. No new matter has been added.

Claim 10 is further rejected for the recitation of “Lin20”. Applicants have amended the claim to remove the recitation “Lin20” to clarify the claim. Lin20 is disclosed in the specification as a linear library having a potential 3.8×10^{25} amino acid diversity (see page 48, lines 1-12). The Lin20 library was constructed to display a single linear peptide in a 20-amino acid template (see page 50, lines 2-3).

Accordingly, withdrawal of the rejection of claim 10 under 35 U.S.C. § 112, second

paragraph is respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 10, 13-26 and 78 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicants respectfully disagree. The Examiner states that “though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the modified polypeptide beyond those disclosed in the examples in the specification” (see Office Action, page 9-10). Applicants disagree. Applicants have described various polypeptides and demonstrated that such polypeptides are capable of binding to KDR or VEGF/KDR complex. Applicants have also adequately disclosed methods for preparing libraries of polypeptides and provided details of how to screen them for their ability to bind KDR or VEGF/KDR using phage display technology, a method well known to those of ordinary skill in the art. Applicants have further provided sequence information of specific polypeptides within each disclosed library (see Table 1, pages 133-142).

Working examples are provided demonstrating that polypeptides generated using the disclosed methods bind KDR or VEGF/KDR. The specific sequences of such polypeptides are also disclosed. For example, sequences identified as belonging to the Lin20 family, SEQ ID NOs:304-310, are demonstrated as capable of binding KDR (see Table 8, page 146 to page 147). Applicants also provide examples of polypeptide sequences capable of binding the KDR/VEGF complex, for example, the Lin20 polypeptide SEQ ID NO:356 is shown to bind the VEGF/KDR complex (see Table 10, page 150).

The specification discloses that “the phage display libraries, such as Lin20, were created to provide a phage population (library) displaying a vast number of different but structurally related amino acid sequences. The amino acid variations are designed to alter the binding properties of the binding peptide or domain without significantly altering its structure (see page 50, lines 18-27).” The structure function relationship is clearly disclosed in that changes to the polypeptide sequences are contemplated that do not significantly affect the structure of the polypeptide but may alter the binding affinity of that polypeptide. Applicants have presented sequences that include specific

modifications as disclosed in the application, such as biotinylation and the inclusion of a JJ spacer (see Table 10, page 150), and have demonstrated that such modified polypeptides retain the ability to bind KDR (see Table 21, page 240). Therefore, Applicants disagree with the Examiner's statement that "the specification is devoid of all modified polypeptides that qualify for functional characteristics claimed" (see Office Action, page 10). Modifications to amino acid sequences are methods known and used widely by those of ordinary skill in the art. The precise structure of each amino acid residue is known and those of ordinary skill in the art are adequately experienced to make modifications to a peptide sequence that does not significantly alter the polypeptide structure and retains or improves the function of that polypeptide. Applicants have provided a means for producing polypeptide sequences and a means for determining the ability of the polypeptide sequences to bind KDR or VEGF/KDR. One of ordinary skill in the art is provided with ample disclosure to allow them to reasonably convey that Applicants had possession of the claimed invention.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

The Examiner rejected claims 10, 13 and 14 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,544,500 (Bittle *et al.*). According to the Examiner, Bittle *et al.* describe a peptide sequence that comprises the sequence Ala-Gln-Lys-Val-Ala encompassed by the consensus sequence disclosed in claim 10.

Applicants respectfully disagree. Applicants have included the "detectable labels or therapeutic agents" recitation of claim 15 in claim 10. Claim 15 was not rejected by the Examiner. Bittle *et al.* demonstrate the antigenic nature of a short peptide that corresponds to a region of foot and mouth disease virus VP₁ protein and that this single peptide sequence is capable of producing a high level of substantially monospecific antigenic activity (see column 5, fourth paragraph). The peptide sequence disclosed by Bittle *et al.* includes a cysteine residue (see Example 1, column 5 and claim 3). The isolated polypeptides of the claimed Lin20 family, are disclosed as a single linear peptide in a 20 amino acid template having amino acids varied at each position in the template to permit any amino acid except cysteine (Cys) (see page 50, lines 2-4). The claims as amended recite

that the polypeptide does not contain any cysteine residues. Therefore, Bittle *et al.* does not anticipate the claimed invention.

The Examiner further indicates that the structure of a peptide sequence confers function and that since the peptide meets the structural limitations it must necessarily and inherently have the functions being claimed (see Office Action, page 11). Applicants respectfully disagree. As described above the peptide sequence disclosed by Bittle *et al.* includes a cysteine residue. The claims specifically recite that the polypeptide does not contain cysteine residues. Therefore, it is clear there can be no inherency when the missing descriptive matter in this instance is the claimed invention as a whole.

The Examiner rejected claims 10 and 13-18 under 35 U.S.C. § 102(b) as being anticipated by Soker *et al.* (Journal of Biological Chemistry, 272(50): 31582-31588 (1997)). According to the Examiner, Soker *et al.* describe purified peptides, VEGF₁₂₁, VEGF₁₆₅ and glutathione S-transferase fusions comprising different segments of exon 7 and exon 8 of VEGF and that the VEGF peptide segment of the fusion peptides can be interpreted to encompass the isolated polypeptide that comprises a modification as disclosed in claim 14.

Applicant respectfully disagrees that the fusion peptides disclosed by Soker *et al.* encompass the isolated polypeptide that comprises modification as disclosed in claim 14. The fusion peptides disclosed by Soker *et al.* are GST-fusion peptides of VEGF exon 7 and 8. The peptide sequences disclosed on page 31585, Figure 5B contain several amino acid substitutions compared to the claimed isolated polypeptides of the invention. Soker *et al.* do not teach or suggest such amino acid modifications.

Further, Soker *et al.* demonstrate that deleting regions of the GST-fusion peptides results in varying changes in the inhibitory ability of these peptides. Soker *et al.* located a “core inhibitory region” within amino acids 22-44 of exon 7. This specific region contains 4 cysteine residues, one of which is indicated to be “crucial for maintaining a specific structure required for the inhibition” (see page 31585, left column, end of the first paragraph). The isolated polypeptides of the claimed Lin20 family are disclosed as a single linear peptide in a 20 amino acid template having amino acids

varied at each position in the template to permit any amino acid except cysteine (Cys) (see page 50, lines 2-4). The claims as amended recite that the polypeptide does not include cysteine residues. The substitutions contemplated in the application are substitutions made with the expectation that the resulting polypeptides would have a similar or improved profile of the described properties (i.e. ability to bind KDR and/or VEGF/KDR). One of ordinary skill in the art would not read the sequences disclosed in Soker *et al.*, which require cysteine residues to maintain their specific structure, to encompass the claimed polypeptides which have no requirement for cysteine and specifically disclose that cysteine residues are not selected as substitutions. Any substitution of the cysteine residue in Soker *et al.* would result in lack of inhibition in the resulting peptide according to Soker *et al.* Thus, Soker *et al.* do not anticipate the claimed invention.

The Examiner further indicates that the structure of a peptide sequence confers function and that since the peptide meets the structural limitations it must necessarily and inherently have the functions being claimed.

Applicants respectfully disagree. As described above, the peptides disclosed by Soker *et al.* require cysteine residues to maintain their structure and function. The claimed polypeptides have no requirement for cysteine residues and specifically disclose that such residues are not selected. One of ordinary skill in the art when reading the disclosure of Soker *et al.* would not infer that said reference teaches the isolated polypeptides that bind to KDR or VEGF/KDR of the instant claimed invention. Therefore, it is clear there can be no inherency when the missing descriptive matter in this instance is the claimed invention as a whole.

The Examiner rejected claims 10 and 13-26 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,984,373 (Wescott *et al.*). According to the Examiner, Wescott *et al.* describe a polypeptide comprising the sequence Trp-Ala-Pro-Cys-Gln-Glu-Glu-Pro-Trp-Leu-Phe-Cys-Phe-His-Gly which encompasses the consensus sequence disclosed in claim 10.

Applicants respectfully disagree. Wescott *et al.* disclose polypeptides capable of binding fibrin as a means for detecting clots. The polypeptide sequence referred to by the Examiner contains cysteine residues. As explained above, the Lin20 family polypeptides are disclosed as a

single linear peptide in a 20 amino acid template having amino acids varied at each position in the template to permit any amino acid except cysteine (Cys) (see page 50, lines 2-4). Further, the claims do not contemplate that any of the amino acid residues in the consensus sequence can be cysteine. Therefore, Wescott *et al.* does not anticipate the claimed invention.

The Examiner further indicates that the structure of a peptide sequence confers function and that since the peptide meets the structural limitations it must necessarily and inherently have the functions being claimed. Applicants respectfully disagree. As described above, the fibrin binding polypeptides disclosed by Wescott *et al.* do not encompass the claimed polypeptides. The polypeptide sequence specifically referred to by the Examiner includes cysteine residues which are specifically not contemplated in the claimed polypeptides. One of ordinary skill in the art would not infer from the teachings of Wescott *et al.* that they teach the isolated polypeptides that bind KDR or VEGF/KDR of the claimed invention.

Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants respectfully request reconsideration. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

A check for a 3 month extension of time is enclosed. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

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